

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62541

Title: Impact of preoperative antibiotics and other variables on integrated microbiome-host transcriptomic data generated from colorectal cancer resections

Reviewer's code: 03478404

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-23 09:19

Reviewer performed review: 2021-01-23 13:58

Review time: 4 Hours

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|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

This complex and original research resulted in an elegant manuscript, written in a nicely manner, containing a lot of very important data from applying an integrative multi-omic analysis of colorectal cancer resection specimens. The overall structure of the manuscript is well respected. The references are pertinent and up-to-date. This original work deserves to be published, after some minor modifications. 1. The title refers only to antibiotic administration before resection, however this research analysed many more aspects. It would not hurt to emphasize these aspects. 2. The Abstract should present the fact that it was a prospective study. Please also insert the period the study was conducted. 3. Core tip presents more explicitly the essence of this research. Maybe data could be harmonized with the Abstract, so that the Abstract appears clearer. It is not only analysing the effect of antibiotic administration before resection (however, this appears as the aim of the study). Maybe the conclusion of the Abstract should be reformulated, given the complex results. 4. Introduction contains the adequate background and it demonstrates why the following five aspects were chosen: tumor histology, preoperative antibiotics, laterality of colorectal cancer location, presence of diabetes mellitus and of Black/African Ancestry race. Please insert the aim of the study by the end of Introduction. Please consider that this research studied much more than the effects of antibiotics (and only 16 [31.4%] of 51 samples were exposed to oral antibiotics, as it appears later in Table 2). 5. Material and methods: please clarify the period the study was performed. Was it 2010-2020? Please also insert here the protocol of using antibiotics (after 2017 - it appears in Introduction - oral neomycin and metronidazole 24 hours in advance of the procedure). In Results (page 11) and Discussion (page 29), however, it appears that antibiotics were also given intravenously 30 minutes before the surgery. Please clarify. Page 7, line 7: Please insert a period after

(0,1,2,3,4). Page 7, line 9 – please replace “was” with “were. Otherwise, this paragraph contains all the necessary data and it is presented in detail, including Statistical analysis. 6. Results are explained clearly, also in tables (3-9) and figures (1-3). Just please remove in the title of Table 3 “between the following groups” – written twice. And please add respective colors to “antibiotics” – Figure 3. Also, please remove (Page 23 – lines 1-2): “Lower detection rates of *F. nucleatum* nusG gene by PCR were previously reported on archived FFPE CRC tissues, ranging from 13%-45% [31,32]” and add it to Discussion. Same for “Expression of the von Hippel-Landau binding protein 1 or VBP1 in Black/AA CRC tumors (n = 64) was also observed to be significantly lower compared to White/EA CRC tumors (n = 284, p = 0.026) in The Cancer Genome Atlas (TCGA) database and in a recently published transcriptomic profiling study[20].” – page 27, lines 6-9. 7. Discussion paragraph could be expanded a bit. Please add “showed/showing” after report – page 29, line 4. 8. Please add Conclusion and Study Highlights. 9. There are no Conflict-of-Interest Disclosure Form and Copyright License Agreement files. Please add. 10. Please also add the STROBE Statement – checklist.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62541

Title: Impact of preoperative antibiotics and other variables on integrated microbiome-host transcriptomic data generated from colorectal cancer resections

Reviewer's code: 03713791

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-22 08:12

Reviewer performed review: 2021-01-25 17:00

Review time: 3 Days and 8 Hours

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |



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SPECIFIC COMMENTS TO AUTHORS

In the present original article Malik et al showed that preoperative antibiotics, given in patients undergoing surgery for colorectal cancer (CRC), change microbiota composition, diversity and transcriptomic profile. Main comments: 1) The main drawback of this manuscript is that the key finding (change in microbiota after antibiotics) is an expected and well known result that does not add any novelty to present knowledge. Authors should have rather investigated another endpoint, for instance whether change in microbiota was effective to prevent peri-operative infections. 2) A real control group of patients without CRC is absent. Normal tissue of patients with CRC is not as reliable as control. 3) What do Authors mean for “tumor histology”? 4) A minor linguistic revision is necessary.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 62541

Title: Impact of preoperative antibiotics and other variables on integrated microbiome-host transcriptomic data generated from colorectal cancer resections

Reviewer's code: 03727521

Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-29 12:54

Reviewer performed review: 2021-02-03 22:09

Review time: 5 Days and 9 Hours

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|---------------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

The authors hypothesize that the antibiotics will impact analysis of multi-omic datasets generated from resection samples to investigate biological CRC risk factors. The aim of the manuscript was to assess the impact of preoperative antibiotics on integrated microbiome and human transcriptomic data generated from archived frozen CRC resection samples. The authors “explored the effect of five variables (tumor histology, preoperative antibiotics, laterality of CRC location, diabetes mellitus, Black/AA race) on analysis of microbiome and host transcriptome among archived frozen CRC resection samples”. As the authors did not only assess the impact of the use of antibiotics on the profile of the intestinal microbiota, I would like to suggest to add these other outcomes in the objectives of the study. The authors studied 51 pairs of frozen sporadic CRC tumor and adjacent non-tumor mucosal samples from 50 CRC patients. As results, it was observed a significant effects of histology ($p = 0.002$) and antibiotics ($p = 0.001$) on microbial β -diversity, increased *Fusobacterium* abundance in tumor vs. nontumor groups and detected significantly reduced bacterial load in the +antibiotics group. The authors emphasized that “there is a measurable effect not only on the tissue-associated microbial communities but also on the host colonic transcriptomic profiles” regarding the use of the antibiotics. But the authors should discuss the clinical importance of this finding, whether if this effect on gut microbiota is permanent or transient since the patient used antibiotics just before surgery. Can we assume that the microbiota will recover some time after using the antibiotic? Or not? Cite some articles about this topic. In conclusion, is an interesting article with original findings that studied the interaction among gut microbiota, use of antibiotics and CRC. I would like to suggest to the authors that they discuss more about the effects of the use of antibiotics on the intestinal microbiota and its implications for the treatment of CRC. In addition, the authors could

discuss the role of the intestinal microbiota in CRC.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 03713791

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Chen-Chen Gao

Reviewer accepted review: 2021-03-04 10:46

Reviewer performed review: 2021-03-04 11:49

Review time: 1 Hour

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection |
| Peer-reviewer statements | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

SPECIFIC COMMENTS TO AUTHORS

The answer regarding negative control is not satisfactory. Indeed, this study lacks a reliable control group that limits the reproducibility

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Position: Peer Reviewer

Academic degree: PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Brazil

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

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Review time: 20 Hours

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
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SPECIFIC COMMENTS TO AUTHORS



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The authors followed the reviewers' recommendations and made the necessary adjustments to the article.

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Reviewer's code: 03478404

Position: Editorial Board

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Professional title: Associate Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: United States

Manuscript submission date: 2021-01-21

Reviewer chosen by: Chen-Chen Gao

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| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
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I am very pleased after attentively reading the new version of this manuscript and the authors' reply. I highly appreciate that the authors performed the corrections and considered my comments, as well as those of the other reviewers (except for the very good remark of the Reviewer nr. 2 – “a real control group of patients without CRC is absent”, but I also agree with the Authors' point of view). Just some comments please: Due to an unknown reason, Tables do not display properly and Figures do not appear at all in the new Word file. Also, there is no STROBE Statement - checklist. The format of the Conflict-of-Interest Disclosure Form is not the requested one (as I can see after downloading). Please double-check and correct. Otherwise, I consider this manuscript having strong points and findings, deserving to be published.